

SUBSTITUTE FORM PTO-1449  
(MODIFIED)U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEATTY. DOCKET NO.  
07662/014001SERIAL NO.  
097089,097INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT  
(Use several sheets if necessary)APPLICANT  
Freire et alFILING DATE  
June 2, 1998GROUP  
2785 1631

(37 CFR 1.98(b))

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL		PATENT NUMBER	ISSUE DATE	PATENTEE	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
msy	AA	5 3 3 1 5 7 3	7/19/1994	Balaji et al	364	500	
msy	AB	5 4 3 4 7 9 6	7/18/1995	Weininger	364	494	
msy	AC	5 6 4 2 2 9 2	6/24/1997	Itai et al	364	494	
msy	AD	5 4 9 5 4 2 3	2/96	DeLisi et al.	364	494	
msy	AE	5 8 5 4 9 9 2	12/98	Shakhnovich et al.	702	27	
msy	AF	5 6 1 2 8 9 5	3/97	Balaji et al.	364	494	
	AG	5 6 4 2 2 9 2	6/97	Itai et al.			
msy	AH	5 8 6 7 4 0 2	2/99	Schneider et al.	364	494	
	AI						
	AJ						
	AK						

## FOREIGN PATENT OR PUBLISHED FOREIGN PATENT APPLICATION

		DOCUMENT NUMBER	PUBLICATION DATE	COUNTRY OR PATENT OFFICE	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	AL							
	AM							
	AN							
	AO							
	AP							

## OTHER DOCUMENTS (Including Author, Title, Date, Place of Publication)

msy	AQ	Abdel-Meguid, Sherin et al, "An Orally Bioavailable HIV-1 Protease Inhibitor Containing an Imidazole-Derived Peptide Bond Replacement: Crystallographic and Pharmacokinetic Analysis", <i>Biochem.</i> , 1994, 33:11671-77
msy	AR	Bailey, David et al, "X-Ray-Crystallographic Studies of Complexes of Pestatin A and A Statine Containing Human Renin Inhibitor with Exdothiapepsin", <i>Biochem.</i> , 1993, 289: 363-371
msy	AS	Baldwin, Eric T. et al, "Structural Basis of Drug Resistance for the V82A Mutant of HIV-1 Proteinase", <i>Nature Struc. Biol.</i> , 1995, 2:244-249

EXAMINER

MG Moran

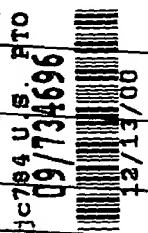
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## OTHER DOCUMENTS (Including Author, Title, Date, Place of Publication)

BA	Baldwin, Robert L., "Temperature Dependence of the Hydrophobic Interaction in Protein Folding", <i>Proc. Nat'l Acad. Sci. USA</i> , 1986, 83:809-8072
BB	Bardi, Jason S. et al, "Structure-Based Thermodynamic Analysis of HIV-1 Protease Inhibitors", <i>Biochem.</i> , 1997, 36:6588-6596
BC	Blundell, T.L. et al, "X-Ray Analyses of Aspartic Proteinases" "The Three-Dimensional Structure at 2-1 Å Resolution of Endothiapepsin", <i>J. Mol. Biol.</i> , 1990, 211:919-941
BD	Brown, Eric D. et al, "Purification of Two Fungal Aspartic Proteinases Using Fast Protein Liquid Chromatography", <i>Agric. Biol. Chem.</i> , 1990, 54:1563-1565
BE	Cabani, Sergio et al, "Group Contributions to the Thermodynamic Properties of Non-Ionic Organic Solutes in Dilute Aqueous Solution", <i>J. Sol. Chem.</i> , 1981, 10:563-595
BF	Cha, Sungman, "Tight-Binding Inhibitors-I" "Kinetic Behavior", <i>Biochem. Pharmac.</i> , 1975, 24:2177-2185
BG	Condra, Jon H. et al, "In vivo Emergence of HIV-1 Variants Resistant to Multiple Protease Inhibitors", <i>Nature</i> , 1995, 374: 569-570
BH	D'Aquino, J. Alejandro et al, "The Magnitude of the Backbone Conformational Entropy Change in Protein Folding", <i>Proteins</i> , 1996, 25:143-156
BI	Dunn, Ben M. et al, "A Systematic Series of Synthetic Chromophoric Substrates for Aspartic Proteinases", <i>Biochem. J.</i> , 1986, 237:899-896
BJ	Erickson, John et al, "Design, Activity, and 2.8 Å Crystal Structure of a C <sub>2</sub> Symmetric Inhibitor Complexed to HIV-1 Protease", <i>Science</i> , 1990, 249:527-529
BK	Fassler, A. et al, "Novel Pseudosymmetric Inhibitors of HIV-1 Protease", <i>Bioorg. Med. Chem. Lett.</i> 1993, 3:2837-2842
BL	Freire, Ernesto et al, "Isothermal Titration", <i>Anal. Chem.</i> , 1990, 62:950-959
BM	Freire, Ernesto et al, "Molecular Basis of Co-Operativity in Protein Folding" <i>J. Mol. Biol.</i> , 1991, 222:687-698
BN	Freire, Ernesto, "Perspectives in Biochemistry and Biophysics", <i>Archives Biochem. Biophys.</i> , 1993, 303:181-184

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## OTHER DOCUMENTS (Including Author, Title, Date, Place of Publication)

ms	CA	Garcia-Moreno, Bertrand E., "Probing Structural and Physical Basis of Protein Energetics Linked to Protons and Salt", <i>Methods Enzymol.</i> , 1995, 259:512-528
ms	CB	Gomez, Javier et al, "The Heat Capacity of Proteins", <i>Proteins: Structure, Function and Genetics</i> , 1995, 22:404-412 (1995)
ms	CC	Gomez, Javier et al, "Thermodynamic Mapping of the Inhibitor Site of the Aspartic Protease Endothiapepsin", <i>J. Mol. Biol.</i> , 1995, 252:337-350
ms	CD	Gomez, Javier et al, "Structural Thermodynamic Study of the Binding of Renin Inhibitors to Endothiapepsin", "Structure and Function of Aspartic Proteinases: Retroviral and Cellular Enzymes", (Eds. James, M.N.G.), Plenum Publishing Co., New York, 1997
ms	CE	Hilser, Vincent J. et al, "Structure-based Calculation of the Equilibrium Folding Pathway of Proteins. Correlation with Hydrogen Exchange Protection Factors", <i>J. Mol. Biol.</i> , 1996(a) 262, 756-772
ms	CF	Hilser, Vincent, J. et al, "The Enthalpy Change in Protein Folding and Binding: Refinement of Parameters for Structure-Based Calculations", <i>Proteins</i> , 1996, 26:123-133
ms	CG	Hilser, Vincent, J. et al, "Predicting the Equilibrium Protein Folding Pathway: Structure-Based Analysis of Staphylococcal Nuclease" <i>Proteins</i> , 1997(a), 27:117-183.
ms	CH	Hilser, Vincent J. et al, "Structure-based Statistical Thermodynamic Analysis of T4 Lysozyme Mutants: Structural Mapping of Cooperative Interactions" <i>Biophysical Chem.</i> , 1997 (b), 64: 69-79
ms	CI	Ho, David D. et al, "Characterization of Human Immunodeficiency Virus Type 1 Variants with Increased Resistance to a C <sub>2</sub> -Symmetric Protease Inhibitor", <i>J. Virol.</i> , 1994, 68:2016-2020
ms	CJ	Hoog, Susan S., "A Check on Rational Drug Design: Crystal Structure of a Complex of Human Immunodeficiency Virus Type 1 Protease with a Novel $\gamma$ -Turn Mimetic Inhibitor", <i>J. Med. Chem.</i> , 1995, 38:3426-3252
ms	CK	Hyland, Lawrence, J., "Human Immunodeficiency Virus-1 Protease. 2. Use of pH Rate Studies and Solvent Kinetic Isotope Effects to Elucidate Details of Chemical Mechanism", <i>Biochemistry</i> , 1991, 30:8454-8463
ms	CL	Iijima, Hiroshi et al, "Calibration of Effective Van Der Waals Atomic Contact Radii for Proteins and Peptides", <i>Proteins</i> , 1987, 2:330-339
ms	CM	Janin, Joel et al, "Conformation of Amino Acid Side-Chains in Proteins", <i>J. Mol. Biol.</i> , 1978, 125:357-386

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Substitute Disclosure Form (PTO-1449)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)  (37 CFR 1.98(b))				APPLICANT Freire et al			
				FILING DATE June 2, 1998		GROUP <del>2785</del> 16 31	
OTHER DOCUMENTS (Including Author, Title, Date, Place of Publication)							
msu	DA	Janin, Joel, "Elusive Affinities", <i>Proteins</i> , 1995, 21:30-39					
msu	DB	Kaplan, Andrew, H., "Selection of Multiple Human Immunodeficiency Virus Type 1 Variants that Encode Viral Proteases with Decreased Sensitivity to an Inhibitor of the Viral Protease", <i>Proc. Natl. Acad. Sci. USA</i> , 1994, 91:5597-5601					
msu	DC	Kauzmann, W., "Some Factors in the Interpretation of Protein Denaturation", <i>Adv. Protein Chem.</i> , 1959, 14:1-63					
msu	DD	Kim, E.E. et al, "Crystal Structure of HIV-1 Protease in Complex with VX-478, a Potent and Orally Bioavailable Inhibitor of the Enzyme" <i>J. Am. Chem. Soc.</i> , 1995, 117:1181-1182					
msu	DE	Kuzmic, Petr, "Program DYNAFIT for the Analysis of Enzyme Kinetic Data: Application to HIV Proteinase", <i>Anal. Biochem.</i> , 1996, 237:260-273					
msu	DF	Larson, Merle K., "Endothia Parasitica Protease. Parameters Affecting Activity of the Rennin-like Enzyme", <i>J. Dairy Sci.</i> , 1970, 53:253-261					
msu	DG	Lee, B. et al, "The Interpretation of Protein Structures: Estimates of Static Accessibility", <i>J. Mol. Biol.</i> , 1971, 55:379-400					
msu	DH	Lee, Kon Ho et al, "Estimation of Changes in Side Chain Configurational Entropy in Binding and Folding: General Methods and Application to Helix Formation", <i>Proteins: Struct. Func. and Genetics</i> , 1994, 20:68-84					
msu	DI	Levitt, Michael, "Energy Refinement of Hen Egg-White Lysozyme", <i>J. Mol. Biol.</i> , 1974, 82:393-420					
msu	DJ	Lin, Yingzhang et al, "Effect of Point Mutations on the Kinetics and the Inhibition of Human Immunodeficiency Virus Type 1 Protease: Relationship to Drug Resistance", <i>Biochem.</i> , 1993, 34:1143-1152					
msu	DK	Luque, Irene et al, "Structure-Based Thermodynamic Scale of $\alpha$ -Helix Propensities in Amino Acids", <i>Biochemistry</i> , 1996, 35:13681-13688					
msu	DL	Madhusoodan, Hosur, V. et al, "Influence of Stereochemistry on Activity and Binding Modes for $C_2$ Symmetry-Based Diol Inhibitors of HIV-1 Protease", <i>J. Am. Chem. Soc.</i> , 1994, 116:847-855					
msu	DM	Murphy, Kenneth P. et al, "Molecular Basis of Co-operativity in Protein Folding. III. Structural Identification of Cooperative Folding Units and Folding Intermediates", <i>J. Mol. Biol.</i> , 1992, 227:293-306					
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OTHER DOCUMENTS (Including Author, Title, Date, Place of Publication)							
msy	EA	Murphy, Kenneth P. et al, "Thermodynamics of Structural Stability and Cooperative Folding Behavior in Proteins", <i>Adv. Protein Chem.</i> , 1992, 43:313-361					
msy	EB	Murphy, Kenneth P. et al, "Structural Energetics of Peptide Recognition: Angiotensin II/Antibody Binding", <i>Proteins: Struc. Func. Genetics</i> , 1993 15:113-120					
msy	EC	Murphy, Kenneth P. et al, "Entropy in Biological Binding Processes: Estimation of Transnational Entropy Loss", <i>Proteins: Struc. Func. Genetics</i> , 1994, 18:63-67					
msy	ED	Rich, Daniel H., "Inhibitors of Cysteine Proteinases", in <i>Proteinase Inhibitors</i> , (eds. Barret & Salvesen) (Elsevier Science Publishers, New York, 1986)					
msy	EE	Rich, Daniel H. et al, "Mechanism of Inhibition of Pepsin by Pepstatin. Effect of Inhibitor Structure of Dissociation Constant and Time-Dependent Inhibition", <i>Biochem. Pharmacol.</i> , 1980 29:2205-2212					
msy	EF	Roberts, Noel A., "Drug-Resistance Patterns of Saquinavir and Other HIV Proteinase Inhibitors" <i>AIDS</i> , 1995, 9:S27-S32					
msy	EG	Schinazi, Raymond F. et al, "Mutations in Retroviral Genes Associated with Drug Resistance", <i>Int. Antiviral News</i> , 1996, 4:95-100					
msy	EH	Smith, Ross et al, "Ionization States of the Catalytic Residues in HIV-1 Protease", <i>Nature Struc. Biol.</i> , 1996, 3:946-950					
msy	EI	Spinelli S. et al, "The Three-Dimensional Structure of the Aspartyl Protease from the HIV-1 Isolate BRU", <i>Biochimie</i> , 1991, 73:1391-1396					
msy	EJ	Straume, Martin et al, "Thermodynamic Strategies for Protein Design: Increased Temperature Stability", In <i>Biocatalysis at Extreme Temperature: Enzyme Near and Above 100°C</i> , (Adams M.W.W. & Kelly R.M., eds) 1992, pp. 122-135, ACS Books, Washington, DC					
msy	EK	Thaisrivongs, Suvit et al, "Structure-Based Design of Novel HIV Protease Inhibitors: Carboxamide-Containing 4-Hydroxycoumarins and 4-Hydroxy-2-pyrones as Potent Nonpeptidic Inhibitors", <i>J. Med. Chem.</i> , 1995, 38:3624-3637					
msy	EL	Thompson, Scott K. et al, "Rational Design, Synthesis, and Crystallographic Analysis of a Hydroxethylene-Based HIV-1 Protease Inhibitor Containing a Heterocyclic P <sub>2</sub> -P <sub>2</sub> Amide Bond Isotere", <i>J. Med. Chem.</i> , 1994, 37:3100-3107					
msy	EM	Tisdale, Margaret, "HIV Protease Inhibitors-Resistance Issues", <i>Int. Antiviral News</i> , 1996, 4:41-43					
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)  (37 CFR 1.98(b))				APPLICANT Freire et al		09/734,686	
				FILING DATE June 2, 1998		GROUP 2785/63/	
OTHER DOCUMENTS (Including Author, Title, Date, Place of Publication)							
msy	FA	Wang, Yun-Xing et al, "Solution NMR Evidence That the HIV-1 Protease Catalytic Aspartyl Groups Have Different Ionization States in the Complex Formed with the Asymmetric Drug KNI-272", <i>Biochemistry</i> , 1996, 35:9945-9950					
		Williams, Jeffrey W. et al, "The Kinetics of Reversible Tight-Binding Inhibition", <i>Methods Enzymol.</i> , 1970, 19:436-467					
msy	FB	Wlodawer, Alexander et al, "Structure-Based Inhibitors of HIV-1 Protease", <i>Ann. Rev. Biochem.</i> , 1993, 179:543-585					
		Xie, Dong et al, "Molecular Basis of Cooperativity in Protein Folding V. Thermodynamic and Structural Conditions for the Stabilization of Compact Denatured States", <i>Proteins: Struct. Func. Genetics</i> , 1994(a) 19:291-301					
msy	FC	Xie, Dong et al, "Structure Based Prediction of Protein Folding Intermediates", <i>J. Mol. Biol.</i> , 1994(b), 24:62-80					
		Whitaker, "Protease of <i>Endothia parasitica</i> " <i>Methods in Enzymol.</i> 19:436-445, 1970.					
msy	FD	Wiseman et al., "Rapid Measurement of Binding Constants and Heats of Binding Using a New Titration Calorimeter" <i>Anal. Biochem.</i> 179:131-135, 1989.					
		<del>Dang, A.M. et al., "Three Dimensional Structure of a Natural Autoantibody: A Predicted Model ..."; Int's Conf. of IEEE Vol. 14, 10/92, pp. 202-203</del>					
msy	FE	<del>Fisher, M.A. et al.; "A Computer Assisted Receptor Mapping Approach to the Design of Anti-AIDS Agents Directed at HIV Reverse Transcriptase"; Proc. of 1993 IEEE 19th Annual Northeast Bioengineering Conf., March, 1993, pp. 162-163</del>					
		<del>Ho, C.M.W. et al., "De Novo Design of Ligands", Proc. of 27th Hawaii Int'l Conf. on System Sciences; Vol. 5, January 1994, pp. 213-222</del>					
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